UNITED STATES DEPARTMENT OF AGRICULTURE

FOOD SAFETY AND INSPECTION SERVICE

THE COMPOUND EVALUATION SYSTEM
SECOND EDITION, REVISED

Developed By

THE RESIDUE EVALUATION AND PLANNING DIVISION

SCIENCE AND TECHNOLOGY PROGRAM

300 12th Street, S. W.
Washington, D. C. 20250

1991

COMPOUND EVALUATION SYSTEM

Introduction

Modern agriculture has benefited from the development of pesticides and animal drugs that have afforded the producer a means of reducing economic losses. In animal feed crops such losses result from damage caused by insects, competing vegetation, or disease; livestock or poultry growers suffer losses due to a number of infectious diseases and parasitic conditions. Consequently, herbicides, pesticides, and prophylactic and therapeutic agents have proved popular in modern agriculture. In addition to these compounds, animal growth-promoting compounds are used to enhance weight gain and feed conversion efficiency.

Livestock and poultry are exposed to chemical products directly, as boluses, injectables, implants, dips, or drenches, or indirectly from residues in feed, forage, or drinking water. In addition, environmentally-persistent agents from past industrial or agricultural practices may appear as residues of concern in meat or poultry.

The Federal Meat Inspection Act and the Poultry Products Inspection Act authorize the U.S. Department of Agriculture (USDA) to inspect meat and poultry transported or offered for sale in interstate commerce. USDA's Food Safety and Inspection Service (FSIS) conducts an inspection program to ensure that meat and poultry products are safe, wholesome, and accurately labeled.

Routine inspection procedures, however, cannot usually determine the presence of chemical residues, unless physical evidence is apparent. It is therefore necessary to perform chemical or microbiological analyses to detect potentially harmful residues. FSIS instituted its National Residue Program (NRP) in 1967 to monitor and control harmful residues in meat and poultry. The NRP is designed to detect, control, and prevent residues of drugs, pesticides and other contaminants in meat and poultry products designated for human consumption. The present residue monitoring strategy of FSIS aims at maintaining a 95 percent likelihood of detecting at least one violation when at least 1 percent of the animal population is violative.

The NRP currently checks for residues of approximately 130 of the pesticide and drug products that may be used in domestically-produced or imported meat and poultry products. The chemicals to be analyzed in FSIS laboratories are selected on the basis of toxicity, exposure level, persistence, and other criteria, such as the existence of established tolerances and the availability of suitable analytic methods. In the domestic monitoring program, random samples are taken from each animal species to test for compliance with tolerance levels for the chemical, and to determine

a nationwide profile of occurrence of residue violations and trends.

The current testing program is described more fully in the FSIS document "Compound Evaluation and Analytical Capability / National Residue Program Plan 1990" (FSIS, 1990).

Need for Compound Evaluation and Ranking

More than 600 pesticides are registered for use in the United States. Pesticide residues may also occur in meat and poultry as the result of environmental contamination. The number of potential residues from animal drugs is equally impressive. The potent biological activity of many of these compounds raises concern regarding the potential hazard to human health.

It is not necessary to monitor for residues of all chemicals, since chemicals differ greatly in ability to produce a residue, degree of hazard to health, and potential for exposing the human population to their residues. In deciding where available resources and testing efforts should be assigned, FSIS must assess relative concerns for those residues most likely to have the greatest impact on public health. Similarly, the allocation of research and development resources must be based on an evaluation of the public health hazard.

Basic Approach to Compound Ranking

The concept of compound ranking is not new. Several ranking approaches have been published (Gervertz et al., 1980; Oller et al., 1980; Von Rumker et al., 1975). The Food and Drug Administration (FDA) has developed two systems: a system for the safety assessment of food and color additives, the 'Red Book' (FDA, 1982), and a surveillance index for evaluating the potential health risks of pesticide residues in food (Reed, 1984). FSIS reviewed these approaches before developing an appropriate system for itself.

A compound ranking system must satisfy certain basic requirements. First, it must provide a well-defined and systematic approach for evaluating data. Second, it must be a manageable and dynamic system that can accomodate new information and permit rapid reassessment of the potential effect on public health of a given compound. Third, it should be sufficiently flexible in the use of scientific judgment to allow definitive decisions to be made even with gaps in desirable information.

FSIS developed a Compound Evaluation System (CES) in 1985 to assist the agency in the effective management of its resources and residue program activities (FSIS, 1988). Under this initial version of the

CES, compounds that can leave residues were ranked both for toxicity and for probability of human exposure. After several years of experience with the CES, the Agency determined that additional criteria were needed in order to select chemicals for our testing program that are most likely to leave a residue. In the revised CES, if the first evaluation element indicates that a residue can be formed, the potential impact on public health is expressed as a function of two other elements: hazard (adverse effects that may be produced by a given compound) and exposure (residue concentration; factors affecting concentration, such as use patterns, withdrawal times, duration of consumption, or frequency of consumption of product containing the residues of concern).

In summary, our basic approach to compound ranking consists of three elements:

1. Determining if a compound can cause a residue;
If the answer is Yes, then,
2. Assessing the hazard of the compound, and
3. Assessing the potential for human exposure resulting from occurrence in meat or poultry.

Element I. **Ability to Leave a Detectable Residue**

The first decision to be made about a compound is to evaluate whether this compound can cause a residue in meat and poultry. If the compound cannot cause a residue, there is no need to go further in the evaluation of hazard or exposure to humans in relation to consumption of meat or poultry. If the compound can cause a residue, a two-tiered ranking of a compound for hazard and exposure is determined so that limited resources can be allocated effectively.

There are two ways in which FSIS can predict the likelihood of a residue occurring.

For one, many compounds have tolerances established by the FDA or the Environmental Protection Agency (EPA). Animal drugs are assessed for hazard and exposure by the FDA Center for Veterinary Medicine; withdrawal times are mandated for these compounds and tolerances are set when the FDA assessment deems it necessary. If a compound is rapidly excreted or leaves very small residue concentrations, FDA may decide that no withdrawal time is necessary and therefore no tolerance is required. For example, with naturally-occurring compounds such as estradiol, any residues that would be found in edible product would be far below safe concentrations set by FDA, and therefore a formal tolerance would be irrelevant. EPA does similar risk assessments for pesticides. This assessment is more complicated since EPA must estimate the residual compound on treated crops and the soil in order to estimate the intake of animals or humans. EPA requests

pharmacokinetic and toxicity data from the manufacturer. Studies on the formation of metabolites are required for food animals so that the hazardous effects of any metabolites formed in the body can be estimated. If the data obtained from animal studies indicate that harmful residues can occur, EPA sets a tolerance.

Secondly, assessment of the pharmacokinetic properties of a compound - the rates of absorption, excretion, and tissue distribution - may be obtained from the literature. Many different endogenous factors affect the occurrence and persistence of chemical residues in meat. These factors include, among others, the absorption and metabolic patterns of a given chemical in animals and persistence in tissues. For example, some pesticides are rapidly biodegraded to non-toxic byproducts and are not likely to present a residue problem.

Thus, FSIS can take advantage of data collection and analysis performed by FDA and EPA in deciding whether residues may occur. If there is no tolerance set, FSIS uses pharmacokinetic analysis to assess possible tissue concentrations.

Each compound is evaluated for its potential to produce residues in meat or poultry, using the following criteria to exclude a compound from further consideration:

1. There is a zero day withdrawal period established by FDA/EPA.
2. The compound is biodegraded rapidly to non-toxic products.
3. The compound is not absorbed, or if absorbed, is excreted rapidly.
4. The specific compound and its metabolites are physically unstable in the environment, e.g. organophosphorous compounds.

Element II. **Hazard Classification**

The second element of the three-tiered evaluation system involves the categorization of compounds according to their potential hazard. In this context, hazard refers strictly to the inherent toxicity of a compound and does not address the probability of human exposure to residues of a given compound. In assessing the potential hazard to human health from residues of a given chemical, primary emphasis is given to residues producing life-threatening, irreversible, or severely debilitating toxic effects. Special attention is focused on chronic toxic effects, i.e., whether a residue is a mutagen, carcinogen, reproductive toxin, or teratogen since the amount of a compound needed to produce acutely toxic effects is not liable to occur in meat. Toxicologic effects, e.g.,

site-specific organ toxicity, immunotoxicity, hematoxicity, are also considered in assessing the overall hazard potential of a compound.

One of the basic requirements for an effective CES is a well-defined and systematic approach for evaluating available data. Thus, in order to make it easier to evaluate critical toxic effects, a toxicological profile format was developed. Information summarized in this format includes findings from both clinical investigations and laboratory studies. If available, clinical observations from well-documented medical or epidemiologic investigations of exposed humans are invaluable in classifying the hazard potential posed by a substance, especially with oral exposure.

Consideration is given to specific populations that might be exposed to a substance, for example, infants and young children. A second subpopulation of special concern is the pregnant woman and her developing fetus. It also has been shown that foodborne xenobiotics such as heptachlor, polychlorinated biphenyls, and lead can be transmitted to the nursing infant via breast milk. As a result of changes in metabolism and toxicokinetics during aging, the elderly may also be more susceptible to the adverse action of ingested substances. One special category is the geographic distribution of environmental contaminants. Compounds, such as selenium, occur inside geographic bounds and thus are localized hazards.

With these considerations in mind, appropriate data largely from laboratory animals are entered in the toxicologic profile and brief summaries of the toxic effect are prepared. Finally, an overall conclusion is reached regarding the potential hazard posed by the compound under review. This includes assigning the compound to one of five hazard categories (A, B, C, D or Z). A compound will be included in a category if one criterion is met; metabolites may be ranked separately if they are more toxic than the parent compounds.

The categories are defined as follows:

Category A

Designation assigned to compounds for which the experimental or clinical evidence demonstrates a high health hazard potential, based on acute or chronic toxicity data. (1) Severe or life-threatening hyperallergenic insults such as anaphylactic shock have been observed. (2) The compound is mutagenic or a confirmed carcinogen. (3) Adverse reproductive effects, or terata have been demonstrated. (4) Irreversible damage to vital functions, such as the hematopoietic system, the immune system, or hepatic or renal systems, has been observed. (5) Permanent, debilitating effects known to drastically reduce the quality of life. (5) Major metabolites are of equal or greater toxicity and are

known to have extended tissue residency times. (6) Acute toxicity is high in experimental animals. (7) Oral LD50 is 25 milligrams per kilogram of body weight (mg/kg b.w.), or less.

Category B

Designation is assigned to compounds for which the experimental or clinical evidence demonstrates a moderate health hazard potential, based on acute or chronic toxicity data. (1) Severe but non-life-threatening hyperallergenic effects. (2) The compound is considered to be weakly mutagenic with evidence of carcinogenicity being limited to a single species, strain, or sex. (3) The compound has caused, or is suspected of causing reproductive disturbances without being teratogenic. (4) Damage to vital functions may be serious but reversible. (5) Metabolites are no more toxic than the parent compound. (6) Acute toxicity is moderate, e.g., oral LD50 is 25-250 mg/kg b.w.

Category C

Designation assigned to compounds for which the experimental or clinical evidence demonstrates a low health hazard potential. (1) Limited to mild hyperallergenic reactions. (2) May be classified as weakly mutagenic but with no evidence of carcinogenicity. (3) Study results show no form of disturbance to the reproductive process in either sex, nor have any teratogenic effects been reported. (4) Damage to vital functions results in no permanent impairment. (5) Absorption of the compound from the gastrointestinal tract is limited. (6) Metabolism is rapid, the major metabolites are less toxic than the parent compound and there is no tissue accumulation. (7) Acute toxicity is low, e.g., oral LD50 is 250-1000 mg/kg b.w.

Category D

Compounds for which evidence demonstrates a negligible health hazard potential. (1) Test results are negative for mutagenicity, carcinogencity, reproductive toxicity, and teratogenicity. (2) No damage to vital functions has been reported. (3) Acute or chronic toxicity is slight, e.g., oral LD50 is greater than 1000 mg/kg b.w.

Category Z

Designation assigned to compounds for which there is insufficient information available to conduct an adequate toxicologic or pharmacologic evaluation. Depending on the circumstances, the Agency may opt to use this convention or may rely on structure-activity relationships in order to assign a compound to a particular hazard category until more definitive information is obtained.

Element III. **Exposure Characterization**

The third element of the three-tiered compound evaluation system is exposure characterization (EC). Its purpose is to assess the factors that will significantly influence the likelihood of human exposure to chemical residues of pesticides, animal drugs, or other contaminants occurring in meat or poultry in concentrations that may affect human health. For most chemical residues that may occur in meat or poultry, the concentrations are low enough that, with few exceptions, adverse health effects are unlikely to occur from single or very infrequent exposures. One exception concerns individuals who have been sensitized to specific compounds, e.g., penicillin or sulfite, to such a degree that even a single exposure to low concentrations of such residues could result in a hyperallergenic response ranging from a minor rash to more serious and potentially life-threatening effects. Otherwise, greater attention is given to the impact of repeated exposure to small quantities of chemical residues.

The National Academy of Sciences (NAS) report on Risk Assessment in the Federal Government: Managing the Process (NAS, 1983) defined exposure assessment as "the process of measuring or estimating the intensity, frequency, and duration of human exposure to an agent currently present in the environment or estimating hypothetical exposures that might arise from the release of new chemicals into the environment." Experience has demonstrated that several variables may affect the accuracy of food-related exposure estimates.

While FSIS agrees with the NAS on exposure assessment, it must be emphasized that, within the scope of the FSIS compound evaluation system, it is not intended, nor considered necessary, to develop detailed, quantitative exposure assessments. Rather, the intent is to assess those factors that will significantly influence the likelihood of a chemical residue occurring in meat or poultry in concentrations that may affect human health.

There are many factors known to affect the occurrence of chemical residues in meat. These include, among others, the nature or extent of actual or probable use, metabolic patterns of a given chemical in animals and plants, persistence in tissues or the environment, and the potential for deliberate or unintentional misuse.

Some pesticides are rapidly biodegraded to non-toxic byproducts and thus are not likely to present a residue problem. Of greater concern are pesticides that persist in the environment, or that undergo metabolic changes, in either plants or animals, resulting in potentially hazardous metabolites with protracted tissue half-lives. With animal drugs, the more food producing animals treated with, or exposed to, a compound, the greater the probability of residues occurring in human diet. The prophylactic use of drugs to control common diseases, such as coccidiosis in

poultry or atrophic rhinitis in swine, results in a higher probability of frequent residue appearances than the specific therapeutic use of a compound for a disease. The biological half-lives and withdrawal times of such drugs are also important factors. In the case of known contaminants, such as polychlorinated biphenyls, pentachlorophenol, cadmium, and lead, the potential for these substances to occur in meat is determined not only by their ubiquity in the environment but also by their persistence and ability to bioaccumulate in living tissues. It is also important to consider the expected distribution of residues among various tissues and their relative significance in the human diet, that is, whether exposure is expected only from meat and poultry products, or whether other dietary sources may be involved.

An exposure characterization (EC) checklist was constructed for use by FSIS reviewers in order to provide a measure of uniformity and standardization in the evaluation of the many variables known to affect the probability of a chemical residue occurring in meat and poultry. After appropriate information has been entered in the EC checklist, the total profile is then evaluated and a decision made regarding the probability of a specific residue occurring in meat or poultry in concentrations that may be significant for human health. Inherent in this decision process is reliance upon scientific judgment, especially in circumstances where data limitations do not permit a well-documented exposure characterization.

Based on an evaluation of information in the EC checklist, the compound under consideration is assigned to one of five exposure categories, 1-4, and Z, designating the probability of residue occurrence in meat or poultry:

Category 1
: Designates a substance with a high probability of exposure of humans to a toxic concentration from meat or poultry, based on known conditions of use/misuse, metabolic patterns in plants, environmental factors, or historical presence.

Category 2
: Designates a substance with a moderate probability of exposure of humans to a toxic concentration from meat or poultry.

Category 3
: Designates a substance with a low probability of exposure of humans to a toxic concentrations from meat or poultry.

Category 4
: Designates a substance with a negligible probability of exposure of humans to a toxic concentration from meat or poultry (e.g., essential nutrients).

Category Z

Designates a substance with insufficient information available to estimate the probability of exposure of humans to a toxic concentration from meat or poultry.

Application of the CES

After a pesticide, animal drug, or environmental contaminant has been determined to produce a residue (Element I), evaluated according to hazard potential (Element II), and probability of exposure to a residue (Element III), the compound is assigned an overall two-tiered ranking in a matrix (Figure 1).

This dual ranking system results in the classification of a given chemical into one of 24 categories. Compounds of greatest concern are designated A-1 (high health hazard potential/high likelihood of residue occurrence); compounds of least significance are designated D-4 (negligible health hazard potential/negligible likelihood of residue occurrence). In the construction of the compound evaluation system, care was taken to avoid the use of exact numerical rankings that could suggest a high degree of precision possibly not justified because of data limitations or assumptions inherent in the ranking process.

CONCLUSION

The CES serves as a guide to FSIS in identifying the relative concern that should be evoked by specific residues in meat or poultry. CES addresses three major questions: Will a compound produce a residue? If so, what is its hazard, and what is the exposure potential for humans from residues in meat and poultry? Compounds with rankings of A-1, A-2, A-3, B-1, B-2 or C-1 are of most concern. The CES will be continually updated to provide FSIS with the information needed for a scientific approach to the control of chemical residues in meat and poultry.

BIBLIOGRAPHY

Biddle, G. N. (1984). Exposure assessments as a tool in regulatory decisions to ensure food safety. J. Toxicol. 21 No. 1-2, 169-180

FDA (1982). Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives used in Food. Center for Food Safety and Applied Nutrition, Food and Drug Administration, U. S. Department of Health and Human Services, Washington, D.C.

FSIS (1990). Compound Evaluation and Analytical Capability / National Residue Program Plan, 1990, (J. Brown, Ed.), U. S. Department of Agriculture, Food Safety and Inspection Service.

FSIS (1988). The Compound Evaluation System., Food Safety and Inspection Service, U. S. Department of Agriculture, Washington, D. C.

Gevertz, J. N., Bild, E., and Sellers, D. W. (1980). Chemical Selection Methods: An Annotated Bibliography. U. S. Environmental Protection Agency, Washington, D. C. 560/TIIS-80-0001.

NAS (1982). Risk Assessment in the Federal Government: Managing the Process. National Academy of Sciences, National Academy Press, Washington, D. C.

Oller, W. L., Cairns, T., Bowman, M. C., and Fishbein, L. (1980). A Toxicological Risk Assessment Procedure: A Proposal for a Surveillance Index for Hazardous Chemicals. Arch. Environm. Contam. Toxicol. 9, pp. 483-490.

Reed, D. V. (1984). The FDA Surveillance Index for Pesticides: Establishing Food Monitoring Priorities Based on Potential Health Risk. Center for Food Safety and Applied Nutrition, Food and Drug Administration, U. S. Department of Health and Human Services, Washington, D. C.

Von Rumker, R. Lawless, E. W., and Meiners, A. F. (1975). Production, Distribution Use, and Environmental Impact Potential of Selected Pesticides. U. S. Environmental Protection Agency, Washington, D. C. EPA 540/1-74-001.

APPENDIX

FSIS
COMPOUND EVALUATION SYSTEM
WORKSHEETS*

* The worksheets serve to organize data as they are accumulated, and as mnemonics to remind the user of important points to look for. It is not intended that all of the blanks be filled in; rather, the worksheet serves to organize data as they are accumulated after reminding the worker of important points to search for.

CHEMICAL IDENTIFICATION

Compound Name: _____

Chemical Name(s): _____

Type: _____ CAS# _____

CES RANK _____

		Date
Reviewers	_____	_____
	_____	_____
	_____	_____

Abbreviations

CAC/FDA - Cancer Assessment Committee, FDA
CAG/EPA - Cancer Assessment Group, EPA
DHHS - Department of Health and Human Services
EPA - Environmental Protection Agency, USA
FDA - Food and Drug Administration, DHHS, USA
IARC - International Agency for Research in Cancer, U.N.
NAS - National Academy of Science, USA
NCI/NTP - National Cancer Institute/National Toxicology Program, NIH, DHHS
U.N. - United Nations
WHO - World Health Organization

I. RESIDUE POTENTIAL

1. Physical and Chemical Properties

a) Molecular weight

b) Melting point

c) Solubility
   1. Water
   2. Solvent
   3. Oil

d) Oil/Water partition coefficient

e) Density

f) Vapor pressure

g) Acid-base properties

Comments:

2. Residue tolerances and intakes for compounds and metabolites.

APPROVED USE IN FOOD: _____ Yes; _____ No

Species	Maximum Acceptable Concentration [a/]

[a/] Tolerance, T; Action Level, AL; Level of Concern, LOC

PESTICIDES AND ENVIRONMENTAL CONTAMINANTS:

Biological half-life in animal tissues:

	TISSUE				
T 1/2	Fat	Muscle	Liver	Kidney	Other (Specify)
< 5 days					
6-15 days					
16-30 days					
31-60 days					
61-90 days					
>91-120 days					
> 120 days					

(Specify species as appropriate, e.g., C, cattle; S. swine; Ch, chickens; T, turkey; etc.)

ANIMAL DRUGS:

Biological half-life in animal tissues of animal drug:

	TISSUE				
T 1/2	Fat	Muscle	Liver	Kidney	Other (Specify)
< 2 days					
1-2 days					
3-5 days					
6-15 days					
16-30 days					
>30 days					

(Specify species as appropriate, e.g., C, cattle; S. swine; Ch, chickens; T, turkey; etc.)

Comments:

3. Metabolic Factors

PESTICIDES AND ENVIRONMENTAL CONTAMINANTS

Bioaccumulates in animal tissues:

Animals: _____ Yes; _____ No

Metabolites/degradation products from animal metabolism a concern:
_____ Yes; _____ No

BIOLOGICAL HALF-LIFE IN ANIMALS

ANIMAL DRUGS:

Metabolic Clearance: _____ < 12 hours; _____12-24 hours

_____ 24-48 hours;_____48-72 hours

_____ > 72 hours

Terminal Residues of Concern:

Parent compound: _____ Yes; _____ No
Free metabolites: _____ Yes; _____ No
Bound metabolites:_____ Yes; _____ No

Comments:

Bioaccumulates in animal tissues:

_____ Yes; _____ No

BIOLOGICAL HALF-LIFE IN ANIMALS _____

Comments:

RESIDUE WILL BE FORMED

_____ Yes; _____ No

II. HAZARD ASSESSMENT - (Toxicological Profile)

1. ACUTE TOXICITY

CRITERIA	DATA REFERENCE
Species Tested	
Route of Exposure	
Sex (M, F, Both)	
Animal Age at Start	
Animal Weight at Start	
Doses Tested	
Animals/Dose	
LD50 Dose	
Lowest Lethal Dose	
Target Organ(s)	

SUMMARY:

2. OTHER ACUTE OR CHRONIC TOXICITY

CRITERIA	DATA REFERENCE
Nature of Test	
Species Tested	
Route of Exposure	
Study Length	
Sex (M, F, Both)	
Animal Age at Start	
Animal Weight at Start	
Doses Tested	
Animals/Dose	
ACUTE EFFECTS	
TARGET ORGAN(S)	
Reversible	
Irreversible	
Dose Response Relationship	
*NOEL Demonstrated	
*LEL Demonstrated	
CHRONIC EFFECTS	
TARGET ORGAN(S)	
Reversible	
Irreversible	
Dose Response Relationship	
*NOEL Demonstrated	

SUMMARY:

*NOEL = No observed effect level; LEL = Lowest effect level

3. MUTAGENICITY

CRITERIA	DATA REFERENCE			
TYPE OF TEST:	W/O Act*	W-Act*	W/O Act	W-Act
1. Gene Mutation				
Bacterial Cells (Ames, Salmonella)				
**SLRL (Drosophila)				
2. Chromosomal Aberrations				
Mammalian Cells in Culture (Lymphoma)				
Mammalian Cell Translocations (Embryo Culture)				
3. Genetic Toxicity				
DNA Damage (Cell Culture)				
Other Test(s)				

SUMMARY:

*W-Act., with metabolic activation; W/O Act., without metabolic activation.
**SLRL (Sex-Linked Recessive Lethal)

4. REPRODUCTIVE TOXICITY AND TERATOGENICITY

CRITERIA	DATA REFERENCE
Species Tested	
Route of Exposure	
Study Length	
Sex (M, F, Both)	
Animals/Dose	
Time of Exposure	
Generations Studied	
Effects on Reproductive Performance	
Reproductive Organ Toxicity	
Maternal Toxicity	
Terata	
Developmental Toxicity	
Dose Response Relationship	
NOEL Demonstrated	

SUMMARY:

5. CARCINOGENICITY

CONFIRMED CARCINOGEN (Yes/No): _____ Animal; _____ Human

Basis of Confirmation: _____
_____
_____

SUSPECT CARCINOGEN (Yes/No): _____ Animal; _____ Human

Basis of Suspicion: _____
_____
_____

Animal Species Tested: _____

Route of Exposure: _____

Tumor Site(s): _____

Tumor Type(s): _____

Dose Response Relationships: _____ Yes; _____ No

NOEL Demonstrated: _____ Yes; _____ No

Virtually Safe Dose Determined: _____ Yes; _____ No

Concentration: _____

References (IARC, CAC/FDA, CAG/EPA, NCI/NTP, OSHA, NAS, Other)

_____

SUMMARY:

5. CARCINOGENICITY (Continued)

CRITERIA	DATA REFERENCE
Species Tested	
Route of Exposure	
Study Length	
Sex (M, F, Both)	
Animal Age at Start	
Animal Weight at Start	
Doses Tested	
Animals/Dose	
Time to Tumor	
Tumor Site	
Tumor Type	
Tumor Incidence	
Dose Response Relationship	
Threshold Dose or NOEL Demonstrated	

SUMMARY:

6. CONCLUSION: _____

HAZARD CLASSIFICATION (Circle one): A B C D Z

III. EXPOSURE CHARACTERIZATION:

Historical presence in FSIS analyses: _____ Domestic _____ Import

Species: _____

Acceptable Daily Intake Established: _____ (WHO, EPA, FDA)

Provisionally Tolerable Intake Established: _____ (WHO, EPA, FDA)

Total Dietary Intake: _____ Adult

_____ Child

_____ Infant

(Ref._____)

Market Basket Content:

Significant Source(s) in Diet _____

---

1. CONDITIONS OF USE:

Approved use in food animals:

_____ Yes; _____ No

Species	Maximum Acceptable Level [a/]

Known/Suspected Misuse

_____ Yes; _____ No

Species:

_____
_____
_____
_____

[a/] Tolerance, T; Action Level, AL; Level of Concern, LOC.

2. NATURE OF USE:

PESTICIDES AND ENVIRONMENTAL CONTAMINANTS:

_____ Pre-Emergence _____ Post-Emergence

_____ Directly on primary/major feedstuff
_____ Only on second/minor feedstuff
_____ Direct application to animals
_____ Application to farm animal premises, or in slaughter facilities.

ANIMAL DRUG:_____ Primary Choice; _____ Secondary Choice

_____ Preventive; _____ Therapeutic; _____
_____ OTC: _____ Rx _____
_____ Major species; _____ Minor species _____
_____ For high incidence disease/parasite conditions
_____ For low incidence disease/parasite conditions
_____ For feed efficiency/use in promoting growth

Stage of Exposure: _____ growing; _____ finishing; _____ mature;

Dosing error: _____ likely: _____ unlikely to result in violative resides.

Cross Contamination: _____ likely; _____ unlikely
Withdrawal Period: _____ none required; _____ 1-2 days
_____ 3-5 days; _____ 6-15 days
_____ 16-30 days; _____ > 30 days

Exposes ≥ 50% of at least 2 major species: _____
Exposes ≥ 50% of at least 1 major species: _____
Exposes ≥ 25% but < 50% of at least 1 major species: _____
Exposes ≥ 10% but < 25% of at least 1 major species: _____
Exposes ≤ 10% of a major species or 25% of a minor species: _____

SUMMARY:

3. METABOLIC/OTHER FACTORS:

PESTICIDES AND ENVIRONMENTAL CONTAMINANTS

_____ Readily degraded
_____ Environmentally persistent
_____ Production volume

Demonstrated systemic plant activity: ____ Yes; ____ No

Residues readily translocate to edible portions: ____ Yes; ____ No

Terminal residues of plant metabolism a concern: ____ Yes; ____ No

Bioaccumulates in Plant Tissues

_____ Yes; _____ No.

Comments:

3. METABOLIC/OTHER FACTORS (Continued):

ANIMAL DRUGS

KNOWN/SUSPECTED MISUSE: _____ Yes; _____ No

Species: _____

_____

_____

_____

Comments:

EXTRA LABEL USE: _____ Yes; _____ No

Comments:

4. OTHER CONSIDERATIONS:

Influence of storage conditions;

- reactions with compounds leached from packaging,

- changes due to fluctuating temperature.

Influence of processing and cooking on residue composition.

5. **CONCLUSION:**

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

EXPOSURE CLASSIFICATION (Circle one): 1 2 3 4 Z

CES Ranking: _____

Comments: